Functional role of miR-155 in physiological and pathological processes of liver injury (Review)

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Abstract. There are several types of liver injury, including alcohol-induced liver injury, drug-induced liver injury, infectious liver injury, cirrhosis, liver ischemia/reperfusion injury and liver failure. In recent years, accumulated data have demonstrated that microRNAs (miRNAs/miRs) may be involved in the occurrence and development of a variety of systemic diseases, such as immune diseases, tumors and nervous system diseases. miR-155 is a key miRNA, which has been studied extensively and has been shown to target different genes. In the present review, the potential effects and mechanisms of miR-155 on the physiological and pathological processes of liver injury were reviewed from the perspective of cell stress, inflammation and activation of fibrosis. In addition, the potential benefits of miR-155 as a therapeutic target and predictor of liver injury were summarized.

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Abbreviations: MCP-1, monocyte chemotactic protein-1; ALD, alcoholic liver disease; mTOR, mechanistic target of rapamycin; Rheb, Ras homolog enriched in brain; LAMP1, lysosomal-associated membrane protein 1; LAMP2, lysosomal-associated membrane protein 2; DILI, drug-induced liver injury; INH, isoniazid; Nrf2, NF-E2-related factor-2; ASH, alcoholic steatohepatitis; NASH, non-alcoholic steatohepatitis; MCD, methionine-choline-deficient; C/EBP-β, CCAAT enhancer-binding protein-β; EMT, epithelial-mesenchymal transition; ERK1, extracellular signal-regulated kinase 1; HSC, hepatic stellate cell; CYP3A, cytochrome P4503A; IRI, ischemia/reperfusion injury; AIH, autoimmune hepatitis; LPS, lipopolysaccharide; TLR, Toll-like receptor; BIC, B-cell integration cluster; NF-κB, nuclear factor-κB; HCC, hepatocellular carcinoma; SOCS1, suppressor of cytokine signaling 1

Key words: microRNA-155, hepatitis, liver injury, hepatic ischemia/reperfusion

Contents

1. Introduction

The liver, as one of the most important solid organs of the body, is involved in multiple physiological processes, such as metabolism, immune responses, detoxification, hematopoiesis and hemostasis (1). As reported by Asrani (2), ~2 million individual succumb to liver disease each year worldwide, of which 1 million succumb to complications of liver cirrhosis and 1 million succumb to viral hepatitis and hepatocellular carcinoma. Therefore, liver disease has some of the highest morbidity and mortality rates worldwide. Common liver diseases include viral hepatitis, cirrhosis, portal hypertension, non-alcoholic steatohepatitis (NASH), acute liver failure (ALF) and drug-induced liver injury (DILI) (3). Notably, the aforementioned types of liver disease can lead to liver damage and, eventually, cause disturbances in the normal metabolism of the liver. The mechanism of liver injury is complex and it is considered to be the result of multiple factors acting alone or in combination (1).

Of significance, microRNAs (miRNAs/miRs) serve a key role in the regulation of gene expression (4). miRNAs are

small endogenous RNAs that regulate numerous physiological and pathological processes by controlling gene expression at the post-transcriptional level (5). Previous studies have demonstrated that various miRNAs have crucial roles in diseases. For example, miR-545/374a were found to be highly expressed in hepatitis B virus (HBV)-related liver cancer. In addition, the HBV genome or HBV X protein led to an increase in the expression of miR-545/374a, which promoted liver cancer cell proliferation, migration and invasion by targeting estrogen-related receptor γ *in vitro*. Furthermore, this previous study verified that miR-545/374a may be used as diagnostic markers due to their association with several clinical characteristics, including histological grade, metastasis and tumor envelope (the boundary between the tumor and other tissues) (6). In another previous study, it was shown that lipopolysaccharide (LPS) induced the activation of macrophages to produce inflammatory miR-210, which inhibited the production of inflammatory cytokines by targeting nuclear factor (NF)-κB1 through a negative feedback loop (7). In addition, Chivukula *et al* (8) revealed that miR-143/145 were simply expressed in the intestinal mesenchymal compartment, and that miR-143 may bind to the target gene insulin-like growth factor binding protein 5 to activate insulin-like growth factor signaling, thereby causing post-injury repair and regeneration of the intestinal epithelium. The aforementioned studies indicated that miRNAs may be involved in the occurrence and development of a variety of diseases through their interaction with target genes, and that they may also be used to predict the treatment status and prognosis of diseases.

miR-155 is a representative multifunctional miRNA processed from the B-cell integration cluster (BIC) gene, which is also known as the miR-155 host gene and is located on chromosome 21 in humans. Previously, the expression of miR-155 was verified to be closely associated with tumorigenesis of various types of cancer, including HCC, breast cancer, colorectal carcinoma, non-small cell lung cancer (9), and was therefore considered to be a carcinogenic miRNA (10). However, further research revealed miR-155 to be one of the most conserved and multifunctional miRNAs, which may be involved in the development of diseases of different systems, including diseases of the breast, and nervous and respiratory systems. Notably, Shi *et al* (11) demonstrated that miR-155-5p accelerated brain injury by targeting dual-specificity phosphatase 14, also known as MKP622, to regulate the NF-κB and MAPK signaling pathways in a rat model of cerebral ischemia/reperfusion injury (IRI) and in oxygen-glucose deprivation/reoxygenation-induced SHSY5Y cells. In addition, Zhang *et al* (12) reported that miR-155 promoted smoke-induced lung damage by targeting suppressor of cytokine signaling 1 (SOCS1), to increase the production of inflammatory protein 2, myeloperoxidase and keratinocyte chemoattractant of macrophage and neutrophils infiltration (12). Furthermore, Kandell *et al* (13) revealed that the number of natural killer (NK) cells and their surface cytotoxic receptors was similar between mice lacking miR-155 and wild-type (WT) mice; however, that number was lower when an AT3 mammary carcinoma line was injected into the subcutaneous tissue of mice lacking miR-155, whereas SH-2 containing inositol 5'polyphosphatase 1 (SHIP-1; a target of miR-155) inhibitors were able to reverse this effect (13). At present, there are ongoing studies regarding the roles and mechanisms of miR-155 in liver injury.

In the present review, the effects of miR-155 on liver injury were summarized according to liver disease type. This will provide a comprehensive understanding of miR-155 and lay the foundations for the prediction of therapeutic status and prognosis for liver injury.

2. Role of miR-155 in viral hepatitis-induced liver injury

Viral hepatitis is a major public health concern worldwide (14), which is caused by the hepatitis A, B, C, D and E viruses (15). Currently, hepatitis B has the highest incidence rate, followed by hepatitis C. According to a 2017 report by the World Health Organization, 350 million individuals were infected with HBV and 170-200 million individuals were infected with hepatitis C virus (HCV) worldwide at this time (16). Furthermore, HBV and HCV are the leading causes of cirrhosis and hepatocellular carcinoma (HCC) development (17). Therefore, the present review summarized the role of miR-155 in HBV-and HCV-induced liver injury.

HBV and miR-155. It is well known that HBV is a partially double-stranded DNA virus that affects 350 million individuals worldwide (16). After HBV enters the body, it replicates and assembles in liver cells, and activates the immune response by altering the liver metabolic function or producing a variety of viral proteins, thus resulting in liver damage (18). Accumulating data have indicated that multiple key molecules and proteins participate in HBV-induced liver injury at different levels, including miR-155. Although liver cells are not immune cells, they can express innate immune receptors. Sarkar *et al* (19) reported that miR-155 was downregulated in HBV-infected liver biopsy and serum samples, as well as in HepG2.2.15 cells (HBV stably replicated liver cancer cell line), and that the expression of toll-like receptor (TLR)7 was positively correlated with that of miR-155. The suggested underlying mechanism was that TLR7 induced the expression of miR-155 through NF-κB signaling, and the upregulation of miR-155 could reduce HBV load by targeting CCAAT/enhancer-binding protein-β (C/EBP-β) in HCC cells (19). Furthermore, Su *et al* (20) demonstrated that the ectopic overexpression of miR-155 promoted activation of the JAK/STAT signaling pathway by targeting SOCS1, and markedly inhibited HBV replication by increasing innate antiviral immunity, including the production of type I interferon (IFN) and the expression of IFN-inducible antiviral genes in hepatocytes. However, another study indicated that miR-155 was increased in HCC cells, and stimulated autophagy by downregulating SOCS1, enhancing Akt phosphorylation and inhibiting mechanistic target of rapamycin (mTOR) phosphorylation through the SOCS1/Akt/mTOR axis, thereby enhancing HBV replication in HCC cells (21). In addition, our previous study indicated that hepatitis B e antigen induced the expression of macrophage miR-155 through the PI3K and NF-κB signaling pathways, and increased the expression and secretion of inflammatory cytokines in macrophages by targeting Bcl-6, SHIP-1 and SOCS-1 to promote liver injury (22). Therefore, miR-155-mediated HBV replication remains controversial, and more research is required to further determine the role

of miR-155 in this process. However, these findings suggested that miR-155 may participate in liver injury by regulating the macrophage-mediated immune response.

HCV and miR-155. Unlike HBV, HCV is a single-stranded hepatotropic RNA virus and the leading cause of chronic hepatitis and liver disease in the world (23,24). HCV-infected hepatocytes lead to liver damage through virus self-replication and the immune response (23). Growing evidence has indicated that miR-155 may affect the replication and life cycle of HCV, and could be employed by host cells and the virus to control or accelerate viral infection. Kałużna (25) showed that miR-155 had an abnormally high expression in HCV-infected patients and induced an inflammatory response. Moreover, even after the completion of antiviral therapy, miR-155 promoted the replication and persistence of the virus. miR-155 was also shown to be related to the inhibition of apoptosis and increased proliferation of hepatocytes, which facilitated the growth of liver cancer (25). Zhang *et al* (10) reported that the levels of the transcriptional co-activator, P300, were increased in HCV-infected hepatocytes, which activated the NF-κB pathway, resulting in aggravated liver damage and enhanced expression of miR-155. In addition, upregulation of miR-155 activated the Wnt/β-catenin signaling pathway by targeting adenomatous polyposis coli (APC), thereby promoting the proliferation of hepatocytes and tumorigenesis (10). In addition, Grek *et al* (26) revealed that the replication of HCV RNA was accompanied by an obvious increase in miR-155 expression. The appearance of the negative strand of the virus RNA was closely associated with a higher level of BIC RNA and Dicer protein in peripheral blood mononuclear cells of patients with chronic HCV (CHC) (26). Jiang *et al* (27) demonstrated that the levels of miR-155 were significantly increased in the liver of HCV-infected patients and were negatively correlated with viral load; however, miR-155 was not correlated with inflammatory grade, fibrosis stage and HCV genotype. In addition, it was demonstrated that the expression of miR-155 was closely associated with the expression of hepatic genes, such as TGF-β, IL-10, TLR3, IFN-stimulated gene 15 and IFN-induced protein with tetratricopeptide repeats 1. Mechanistically, this previous study demonstrated that NF-κB-controlled miR-155 abrogated the immunosuppressive effects of TGF-β and IL-10 on TLR3-mediated antiviral activity in murine Kupffer cells (KCs) and sinusoidal endothelial cells to promote liver injury (27). Furthermore, it has been shown that TLR4 and TLR8 ligands, as well as non-structural (NS)3, NS5 and HCV core proteins, can induce miR-155 expression and TNF-α production in human monocytes. A statistically significant increase in the serum levels of miR-155 was observed in patients with chronic HCV infection compared with those in the normal controls, which may be an indicator of inflammation-caused liver damage (24). Cheng *et al* (28) verified that the expression levels of T-cell immunoglobulin mucin-3 (Tim-3) and T-box expressed in T cells (T-bet) were upregulated, whereas those of miR-155 were downregulated in NK cells following HCV infection. The reconstitution of miR-155 by transfecting its mimics resulted in a decrease in Tim-3 and T-bet expression and an increase in the levels of IFN-γ in NK cells by promoting the phosphorylation of STAT5 (28). These findings suggested that miR-155 may not only affect virus replication by regulating the function of liver parenchymal or non-parenchymal cells, but may also enhance immune cell function to cause liver damage or accelerate the proliferation of hepatocytes and inhibit their apoptosis, thereby initiating the occurrence of liver cancer.

3. Role of miR-155 in alcohol- and drug-induced liver injury

An increasing number of individuals abuse alcohol and drugs, which are linked to >200 diseases (29). The liver is the main organ of alcohol and drug metabolism; therefore, alcoholic liver injury and/or DILI are serious clinical problems and among the leading causes of ALF-related mortality (29,30).

Alcoholic liver injury and miR-155. Excessive drinking over a long period of time can lead to inflammation in several organs, including the liver and brain (31). A previous study demonstrated that alcohol consumption induced miR-155 expression in mice, and miR-155 deficiency protected mice from alcohol-mediated inflammation by inhibiting an increase in the cytokines, monocyte chemoattractant protein-1 (MCP-1) and TNF-α (31). Long-term and chronic drinking have been shown to increase the sensitization of KCs to gut-derived LPS stimulation and lead to more severe inflammatory responses in the liver (29). Given the potential effect of miRNAs on LPS-induced macrophage activation, Bala *et al* (32,33) demonstrated that chronic alcohol treatment induced a time-dependent increase in the levels of miR-155 in macrophages *in vivo* and *in vitro*, which was linearly correlated with TNF-α production. Furthermore, alcohol pretreatment enhanced the LPS-induced expression of macrophage miR-155. Mechanistically, it was indicated that activation of the NF-κB signaling pathway upregulated miR-155 expression, which contributed to alcohol-induced TNF-α production by enhancing the stability of its mRNA via the human antigen R protein (32,33). In addition, based on the increased miR-155 expression in the hepatocytes of alcohol-fed mice compared with pair-fed mice, Bala and Szabo (33) revealed that overexpression of miR-155 in mouse primary hepatocytes led to a decrease in SOCS1 and C/EBP-β proteins, which participate in alcoholic liver disease (ALD) as tumor suppressors and mediators of oxidative stress (33). In addition, Babuta *et al* (34) identified an autophagic and exosomal function disorder in ALD and alcoholic hepatitis by detecting p62 and LC3-II levels. Secondly, it was demonstrated that alcohol-induced miR-155 could target and inhibit mTOR, Ras homolog enriched in brain (Rheb), lysosomal-associated membrane protein (LAMP)1 and LAMP2 activity of macrophages and hepatocytes to impair autophagic flux, thereby facilitating exosome release and inducing autophagy to remove pathogenic or damaged proteins and nucleic acids to accelerate liver injury (34). Therefore, miR-155 may affect alcohol-induced liver injury mainly through cellular oxidative stress, inflammatory cytokine production, exosome biosynthesis and autophagy.

DILI and miR-155. DILI is a disease that occurs mainly in individuals who have been exposed to certain drugs, herbs or dietary supplements; DILI poses a serious threat to patient

health and is an important issue that needs to be taken into consideration during drug development (30). The mechanism underlying DILI is primarily immune-mediated and is often associated with genetic risk determined by human leukocyte antigen variation (35). In severe cases, it may lead to hospitalization, and even liver failure, liver transplantation or death. DILI often shares symptoms with a variety of acute and chronic diseases, including hepatitis, cholestasis, steatosis and fibrosis (36). From a mechanistic point of view, it mainly includes the failure of drug metabolic pathways, cell death, the recruitment and activation of inflammatory leukocytes, such as monocytes and lymphocytes, and the activation of local immune cells, such as KCs (37). miR-155 has been reported to participate in the occurrence and development of DILI through the aforementioned mechanisms. For example, Yuan *et al* (38) reported that the levels of miR-155 were markedly enhanced in the liver and blood following the administration of acetaminophen. Conversely, miR-155 knockout activated NF-κB by enhancing p65 signaling and abnormal expression of IκB kinase (a direct target of miR-155), which increased serum aspartate aminotransferase and alanine aminotransferase (ALT) levels, and significantly increased the levels of various inflammatory mediators, such as TNF-α and IL-6, leading to a further deterioration of liver injury (38). Therefore, it was hypothesized that the significantly upregulated miR-155 following acetaminophen treatment may protect individuals from acetaminophen-induced liver damage. In addition, anti-tuberculosis (TB) drugs have been shown to induce liver injury, which constitutes a serious side effect of TB therapy and may negatively affect patient compliance (39). Isoniazid (INH) is a first-line medication for TB; however, hepatotoxicity is a frequent adverse effect of INH that may promote the progression of liver cirrhosis (40). Song *et al* (41) demonstrated that the expression of miR-155, participating in endotoxin shock caused by lipopolysaccharide/TNF-α (42), was increased in mice treated with INH, which in turn enhanced the expression of TNF-α by regulating the Fas-associated death domain and exacerbated liver damage by increasing the inflammatory response. Furthermore, Wan *et al* (43) revealed that the synthetic chemical compound perfluorooctanesulfonic acid (PFOS) resulted in hepatotoxicity after accumulating in the liver, and significantly upregulated miR-155 expression by activating reactive oxygen species in liver cells. The inhibition of miR-155 further reduced cytotoxicity and oxidative stress in hepatocytes exposed to PFOS exposure by targeting the NF-E2-related factor 2 (Nrf2) signaling pathway to prevent oxidative liver damage (43). These findings indicated that miR-155 may target multiple genes, and play an essential role in DILI through cellular inflammatory responses and oxidative stress.

4. Role of miR-155 in steatohepatitis-induced liver injury

Steatohepatitis includes ASH and NASH, with the latter accounting for the vast majority of steatohepatitis cases (44). NASH is characterized by a difficult diagnosis, complex pathogenesis and lack of recognized treatment (45). Previous studies have shown that type 2 diabetes, obesity and older age are common risk factors for NASH (44,45). In NASH, miR-155 is considered an important inflammatory regulator (46). Wang *et al* (44) reported that the levels of miR-155 were significantly decreased in the liver and peripheral blood of patients with NASH compared with those in healthy controls. TargetScan and dual-luciferase reporter assay verified that liver X receptor α was a target for miR-155, which was found to decrease the hepatic lipid content and protein expression of sterol regulatory element-binding protein 1 and fatty acid synthase thus alleviating steatohepatitis (44). In addition, the expression of miR-155 was increased in hepatocytes and liver mononuclear cells in steatohepatitis mice fed a methionine-choline-deficient (MCD) diet. Conversely, miR-155 deficiency attenuated liver steatosis and fibrosis, but did not prevent liver inflammation and injury in MCD-induced steatohepatitis. In addition, the activation of SMAD family member 3 and C/EBP-β was found to be regulated by miR-155 in steatohepatitis-induced liver fibrosis (47). Based on these aforementioned studies, the different effects of miR-155 on NASH may be due to the different research models they adopted. The former (44) used a high-fat diet (HFD) model, whereas the latter (47) used a MCD model. Although a HFD can induce steatosis, inflammation is less prominent and there is no or very little fibrosis compared with that induced by a MCD diet. The necrotic inflammatory changes and fibrosis of MCD-steatohepatitis are more serious and rapid. However, it is certain that miR-155 may affect steatohepatitis mainly through cellular stress responses and activation of fibrosis. In addition, increased expression of miR-155 in murine non-alcoholic fatty liver disease compared with control suggested that miR-155 may regulate the biological process of lipid metabolism (48).

5. Role of miR-155 in liver cirrhosis

Cirrhosis is a common liver injury that, in several cases, can lead to liver cancer and is a cause of increased morbidity and mortality in developed countries (49). It is well known that epithelial-to-mesenchymal transition (EMT) and the extracellular signal-regulated kinase 1 (ERK1) signaling pathway serve key roles in the activation of hepatic stellate cells (HSCs) (50,51). Dai *et al* (52) demonstrated that miR-155 can bind to the 3'-untranslated region (UTR) of transcription factor 4 and angiotensin II receptor type 1, which can enhance the ERK1 signaling pathway to inhibit EMT. It was further identified that the expression of miR-155 was decreased in clinical samples of HSCs, serum and liver tissues from patients with cirrhosis; therefore, the inhibition of miR-155 expression promoted the activation of HSCs, aggravating the occurrence of liver fibrosis (52). It was previously demonstrated that cirrhosis was related to a reduced activity of hepatocyte cytochrome P4503A (CYP3A) (53); however, its pathogenesis has not been elucidated. Whether miR-155 is associated with decreased CYP3A activity is unclear. Vuppalanchi *et al* (54) reported that some underlying etiology (such as HCV, alcohol and insulin resistance), liver inflammation or fibrosis may lead to an increase in the expression of liver miR-155 in patients with cirrhosis, which further interfered with CYP3A translation and synthesis, resulting in decreased CYP3A activity to exacerbate liver cirrhosis (54). Therefore, miR-155 may function in cirrhosis by affecting HSC activation and CYP3A activity.

Table I. Potential regulatory effector and target genes of microRNA-155 in liver diseases.

Disease	Levels in circulation	Levels in liver	Levels in immune cells	Identified targets (Refs.)
Hepatitis B	↓	↓	↑ (Macrophages)	TLR7, C/EBP-β (19), SOCS1 (20-22), BCL-6, SHIP-1 (22)
Hepatitis C	↑	↑	↓ (Natural killer cells)	APC (10), TGF-β, IL-10 (27), Tim-3/T-bet (28)
Alcoholic liver disease	Unknown	↑	↑ (Macrophages)	MCP-1, TNF-α (31), SOCS1, C/EBP-β (33), mTOR, Rheb, LAMP1, LAMP2 (34)
Drug-induced liver disease	↑	↑	Unknown	P65, IKK (38), Fas (41,42), Nrf2(43)
Non-alcoholic steatohepatitis	↓	↓	Unknown	LXR (44), Smad3, C/EBP-β (47)
Liver cirrhosis	↓	↓↑	Unknown	TCF4 (52), CYP3A (54)
Ischemia/reperfusion-injury	↑	↑	↑ (Macrophages)	SOCS1 (56, 58)
Autoimmune hepatitis	Unknown	↑	↑ (Macrophages)	SOCS1, SHIP1 (61)
Septic liver injury	Unknown	↑	Unknown	Nrf-2 (66), MCPIP1 (67)
Liver failure	↑	↑	Unknown	IL-6/TNF-α (70)

6. Role of miR-155 in hepatic ischemia-reperfusion-induced liver injury

IRI has attracted considerable attention worldwide. IRI includes two stages, namely direct cellular injury caused by ischemia, and delayed cell injury and dysfunction caused by reperfusion-mediated inflammation (55). This dynamic process can affect the function of multiple organs, including the lung, kidney, liver, intestine, pancreas, adrenal gland and myocardium. Furthermore, severe IRI may lead to multiple organ dysfunction syndrome (56). Liver IRI is mainly caused by liver transplantation, resection surgery and hemorrhagic and/or septic shock (57). It has previously been reported that miR-155 deficiency can protect mice from liver IRI, as determined mainly by the low levels of hepatocyte apoptosis, serum ALT and Suzuki scores (56). With regard to the exact mechanism, data have shown that M2 macrophages exhibit higher levels of IL-10, and lower levels of IL-6, TNF-α and IL-12p40, to promote either the resolution of inflammation or tissue recovery/healing, as a response to IRI-mediated innate immune stimulation. Meanwhile, the T helper 17 (Th17) response and Th17 differentiation can relieve liver IRI, which has been verified by the suppression of IL-17 with an anti-IL-17 antibody (56). Tang *et al* (56) and Tan *et al* (58) demonstrated that miR-155 can bind to the 3'-UTR of SOCS1 to promote NF-κB activation, which thus affects the development of M2 macrophages and Th17 differentiation. Additionally, Li *et al* (59) reported that miR-155 deficiency destroyed the balance of M1/M2 macrophages, resulting in a switch to an anti-inflammatory phenotype, where the production of proinflammatory cytokines was decreased, IL-10 was increased, and the expression levels of CD80, CD86 and MHC-II were restrained in KCs after ischemia/reperfusion, thus reducing hepatocyte apoptosis in a co-culture system. The expression of miR-155 in the liver and macrophages is significantly upregulated during the hepatic ischemia-reperfusion-induced liver injury (58,59). Therefore, in addition to ischemic preconditioning to prevent IRI (60), miR-155 antagonists may be used to weaken IRI to some extent.

7. Role of miR-155 in other types of liver injury

Additional types of liver injury include autoimmune hepatitis (AIH), septic liver injury and liver failure. The present review aimed to explain the significant role of miR-155 in their pathogeneses.

AIH and miR-155. AIH is a chronic, progressive autoimmune disease characterized by liver inflammation, elevated transaminase levels and the activation of intrahepatic lymphocytes (61,62). A previous study reported that the expression levels of miR-155 were increased in peripheral blood monocytes and liver tissues from patients with AIH. The dominant mechanism is that miR-155 can regulate the differentiation and recruitment of Th17/regulatory T (Treg) cells by targeting SOCS1 and SHIP1. Inhibition of miR-155 may inhibit Th17-mediated expression and secretion of pro-inflammatory IL-10, but not Treg-mediated production of anti-inflammatory IL-10, thus suggesting that miR-155 may accelerate liver damage (61). Thus, miR-155 may be a regulator of AIH affected by adaptive immunity, and miR-155 antagonists may be used to inhibit the occurrence of AIH to a certain extent.

Septic liver injury and miR-155. During sepsis, the liver is particularly vulnerable to damage (63). Severe sepsis-induced liver injury may subsequently lead to multiple organ dysfunction syndrome (64). It has been reported that miR-155, upregulated in septic liver injury, may serve a pivotal role (65,66). Yang *et al* (65) reported that antagomiR-155 relieved LPS-induced septic liver injury, as determined by the improved body weight and survival rate of mice, by restraining the infiltration of inflammatory cells and necrosis of liver

cells, and suppressing ALT levels (65). Mechanistically, this previous study revealed that antagomiR-155 alleviated liver injury through controlling mitochondrial dysfunction, oxidative stress-mediated ER stress and hepatocyte apoptosis by targeting Nrf2, and enhancing SOCS1 expression and deactivating JAK/STAT signaling (65,66). Furthermore, Li *et al* (67) demonstrated that, following exposure to LPS, the expression levels of MCP-1-induced protein-1 in macrophages were significantly upregulated, leading to a marked downregulation of miR-155 expression. This resulted in the upregulation of RAR-related orphan receptor α, which reduced the inflammatory response by regulating NF-κB signaling, and thus alleviated the symptoms of septic liver injury (67). These results suggested that miR-155 may serve as a therapeutic target in septic liver injury.

Liver failure and miR-155. According to the speed of disease development, liver failure can be divided into acute, subacute, chronic plus acute, and chronic liver failure. Liver failure generally refers to ALF. During ALF, circulating proinflammatory cytokines, including IL-6, TNF-α, IL-1-β, IL-12, IL-10 and IFN-γ, are regulated by immune cascade activation following LPS binding to TLR4 (68). This leads to marked hepatocyte apoptosis/necrosis due to an excessive immune response, which is severely life threatening (69). Zhang *et al* (70) demonstrated that hepatic miR-155 expression is increased at all time points in the livers of mice with ALF induced by LPS or D-galactosamine + TNF-α, and was associated with IL-6/TNF-α expression (70). Therefore, miR-155 may also be used as a therapeutic target for liver failure.

8. Future prospects

As a multifunctional miRNA, miR-155, which has been widely studied, is known to be involved in a variety of pathophysiological processes via regulation of the expression of target genes, including the occurrence and development of diseases, such as immune diseases, inflammation and cancer. As shown in Table I, the present review indicated that miR-155 may participate in the occurrence and development of liver injury by affecting the function of liver parenchymal cells, non-parenchymal cells or blood-derived immune cells, and by regulating liver inflammation, oxidative stress, lipid metabolism and fiber synthesis. Compelling evidence has confirmed that miR-155 may be considered as a new indicator for the diagnosis, treatment, evaluation of treatment and the monitoring and prognosis of liver diseases. As a reliable biomarker, miR-155 may facilitate the management of liver diseases.

Certain challenges remain with regard to the use of miR-155 for the diagnosis and treatment of liver injury-related diseases: i) The expression, mechanism and targets of miR-155 in the early, middle and late stages of liver injury-related diseases may be different; ii) there are differences in the expression, mechanism and target of miR-155 in the serum or liver tissue, or in different types of parenchymal or non-parenchymal cells in the liver; and iii) although there are several methods of knocking out or overexpressing miRNAs *in vivo* (such as transgenic or gene knockout models, the use of vectors inducing overexpression or interference, ago- or antago-miRNAs, mimics or inhibitors), all of these methods have certain limitations when used in clinical treatment. Therefore, if miR-155 is to be used for the clinical diagnosis and treatment of liver injury-related diseases, further research on liver injury-related diseases, as well as the development of related ancillary technologies and methods, are required.

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Authors' contributions

The conception and design of the work was the responsibility of HB, XF, JB and JQ. The acquisition, analysis, and interpretation of data was performed by XF, JB, CS, JL, HJ and MT. XF, JB and HB drafted the manuscript. Critical revision for important intellectual content was performed by XT, LX, CQ, JQ and HB. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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